1. Drug A is administered as a 250 mg IV bolus dose. 2 hours after administration the concentration in plasma is 4 mg/L and 10 hours after administration the concentration in plasma is 1 mg/L. This lipophilic drug is cleared by the liver and this patient has a liver blood flow of 80 L/hr. The tissue protein binding is 0.6.

A. Calculate $C_0$ (2 pts)

$$K_c = -\text{slope}$$
$$C = C_0 \times e^{(-K_c \times t)}$$

$$C_0 = \frac{C}{e^{(-K_c \times t)}}$$

$$C_0 = 4 \text{ mg/L} \times e^{(-0.173 \text{ hr}^{-1} \times 2 \text{ hr})} = 5.65 \text{ mg/L}$$

B. Calculate $V_d$ (1 pts)

$$V_d = \frac{\text{Dose}}{C_0}$$

$$V_d = \frac{250 \text{ mg}}{5.65 \text{ mg/L}} = 44.2 \text{ L}$$

C. Calculate $f_u$ (1 pts)

$$V_d = V_p + V_t \left( \frac{f_u}{f_{ut}} \right)$$

$$f_u = \left( \frac{V_d - V_p}{V_t} \right) \times f_{ut}$$

$$f_u = \left( \frac{44.2 \text{ L} - 3 \text{ L}}{38 \text{ L}} \right) \times 0.4 = 0.43 \approx 0.4$$

D. Is this a high extraction drug or low extraction drug? (1 pt)

$$C_l = K_c \times V_d$$

$$C_l = 0.173 \text{ hr}^{-1} \times 44.2 \text{ L} = 7.65 \text{ L/hr}$$

If this drug were a high extraction drug, than the clearance would be close to liver blood flow, 80L/hr. However, it is much lower indicating that this drug is a low extraction drug.

E. If this drug were coadministered with Drug B, which is know to caused enzyme induction for the enzymes responsible for the metabolism of Drug A, would you expect to see a change in clearance? (1 pt)

Yes, this would change clearance. Since clearance of a low extraction drug is dependent on the fraction of free drug in plasma and the intrinsic clearance an enzyme induction would increase clearance.

2. How will the following parameters change for a drug that is a high extraction drug eliminated by hepatic clearance only if the free fraction in plasma is changed form 0.8 to 0.2. Indicate increase, decrease, or remain the same (half point each).

A. $V_d$ decrease
B. $E_H$ remain the same
C. $C_l$ remain the same
D. $K_c$ increase
3. Administration of phenobarbital (60 mg daily) to a patient receiving dicumarol (75 mg daily) chronically, reduces the plasma concentration of the anticoagulant (black circle) and the prothrombin (open circle) time, a measure of its effect on the concentration of the vitamin k₁-dependent clotting factors. (2pts)

![Graph showing the interaction between plasma dicumarol concentration and prothrombin time over time.](image)

What kind of pharmacokinetic interaction is responsible for the observed pharmacodynamic interaction? Explain your answer.

Note:
1) Dicumarol is an anticoagulant
2) Prothrombin time is a measure of its effect

From 45-75 days phenobarbital is given. This induces the metabolism of dicumarol, thus decreasing its concentration. As the concentration of dicumarol decreases, it will be easier for the blood to coagulate. Hence, the prothrombin time (which is directly related to the time necessary for the blood to coagulate) will decrease. After 75 days the phenobarbital is not given hence we see the rise of dicumarol concentration and hence an increase in prothrombin time. After 160 days again phenobarbital is given causing again a decrease in dicumarol concentration and after phenobarbital administration is stopped (i.e. after 170 days) the concentration of dicumarol rises. Note that as the 2nd duration of phenobarbital administration is less, the overall decrease in dicumarol concentration for the second time is also less.